

Risk of Transmission of Bovine Spongiform Encephalopathy to Humans in the United States

Report of the Council on Scientific Affairs

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THE TRANSMISSIBLE SPONGIFORM encephalopathies (TSEs) are chronic, progressive, and always fatal neurodegenerative disorders of both animals and humans.^{1,2} They are caused by a slow-replicating agent that requires long incubation periods for disease expression.^{3,4} Animal TSEs include the sheep disease, scrapie, and the cow disease, bovine spongiform encephalopathy (BSE). Human TSEs include Creutzfeldt-Jakob disease (CJD), kuru, and Gerstmann-Sträussler-Scheinker syndrome. In 1995, a novel form of CJD named "new variant CJD" (nv-CJD) was described in the United Kingdom.⁵ This new variant may be due to the transmission of BSE to humans; this has caused significant concern about the potential that many humans may be infected with this disease but are currently asymptomatic.⁶ This report examines the risk of BSE to public health in the United States.

METHODS

The MEDLINE, EMBASE, and Lexis/Nexis databases were searched for articles from 1975 through 1997 on

Context The risk of possible transmission of bovine spongiform encephalopathy (BSE) in the United States is a substantial public health concern.

Objective To systematically review the current scientific literature and discuss legislation and regulations that have been implemented to prevent the disease.

Methods Literature review using the MEDLINE, EMBASE, and Lexis/Nexis databases for 1975 through 1997 on the terms *bovine spongiform encephalopathy*, *prion diseases*, *prions*, and *Creutzfeldt-Jakob syndrome*. The Internet was used to identify regulatory actions and health surveillance.

Data Extraction MEDLINE, EMBASE, and Lexis/Nexis databases were searched from 1975 through 1997 for English-language articles that provided information on assessment of transmission risk.

Results Unique circumstances in the United Kingdom caused the emergence and propagation of BSE in cattle, including widespread use of meat and bone meal cattle feed derived from scrapie-infected sheep and the adoption of a new type of processing that did not reduce the amount of infectious prions prior to feeding. Many of these circumstances do not exist in the United States. In the United Kingdom, new variant Creutzfeldt-Jakob disease probably resulted from the ingestion of BSE-contaminated processed beef. The United Kingdom and the European Union now have strong regulations in place to stop the spread of BSE. While BSE has not been observed in the United States, the US government has surveillance and response plans in effect.

Conclusions Current risk of transmission of BSE in the United States is minimal because (1) BSE has not been shown to exist in this country; (2) adequate regulations exist to prevent entry of foreign sources of BSE into the United States; (3) adequate regulations exist to prevent undetected cases of BSE from uncontrolled amplification within the US cattle population; and (4) adequate preventive guidelines exist to prevent high-risk bovine materials from contaminating products intended for human consumption.

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the terms *bovine spongiform encephalopathy* (BSE), *prion diseases*, *prions*, and *Creutzfeldt-Jakob syndrome* for English-language articles pertinent to the risk assessment issues: (1) identification; (2) assessment; (3) management; and (4) communication, where the hazard or risk was BSE and its transmission. Regulatory actions and health surveillance were located on

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the Internet and last updated in March 1999.

NATURE OF THE INFECTIOUS AGENT

Over the last decade, the "prion hypothesis," which proposes that the agent responsible for TSEs is an infectious protein, has gained support.^{2,7,8} Prions normally exist as protease-sensitive, glycosylphosphatidyl inositol-anchored cell surface proteins in neurons (designated PrP^c or PrP^{Sc}).^{2,9} Disease occurs when an abnormal, protease-resistant isoform (PrP^{Sc} or PrP^{Prs}) accumulates within the brain.^{2,10-12} Transgenic mouse and physical and biochemical studies support the prion hypothesis.¹³⁻¹⁶ The remarkable ability of this infectious agent to survive UV radiation and other procedures designed to hydrolyze and destroy nucleic acids provides further support.¹⁷⁻¹⁹

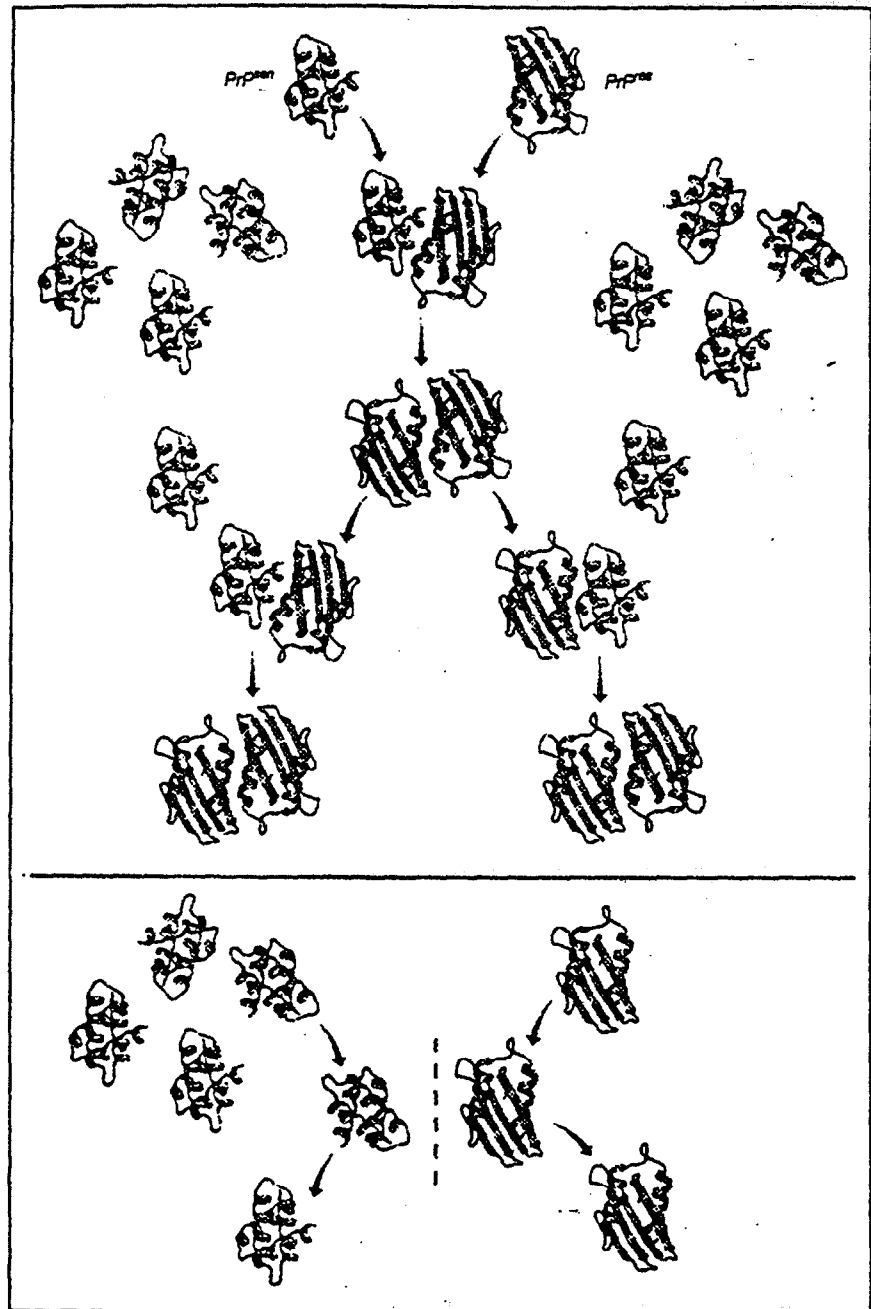
A gene within the host codes for the prion protein.²⁰⁻²² Thus, transgenic mice not expressing the cellular prion protein gene, PrP^c , are resistant to prion disease.²³ As slow conversion of the existing cellular PrP^{Sc} into abnormal PrP^{Prs} progresses, PrP^{Prs} accumulates in the brain.¹⁰ When sufficient particles of PrP^{Prs} accumulate, classic symptoms of spongiform encephalopathies develop.^{24,25} Transmission of the disease, however, can occur before clinical signs appear.^{24,25}

In 1967, Griffith⁷ proposed that the physical association of PrP^{Prs} with its normal homolog PrP^{Sc} forms various heteromers (conformations that involve multiple units of both PrP^{Sc} and PrP^{Prs}). These heteromers are catalyzed by the abnormal PrP^{Prs} into several monomers of abnormal PrP^{Prs} . These new PrP^{Prs} molecules then continue to associate with additional PrP^{Sc} protein and convert them into abnormal PrP^{Prs} (FIGURE 1).^{7,26} Because physical association of PrP^{Sc} and PrP^{Prs} is required, conformational differences between the infecting PrP^{Prs} and the host PrP^{Sc} ultimately determine the efficiency of conversion of the host PrP^{Sc} by the infecting PrP^{Prs} .^{27,28} Thus, if the infecting PrP^{Prs} is dramatically differ-

ent from the host PrP^{Sc} , disease is less likely to occur because the 2 proteins are less likely to associate produc-

tively.^{28,29} The newly synthesized PrP^{Prs} are species-specific and dependent on the origin of the infecting prion.²⁸

Figure 1. Schematic Representation of Conversion of Normal Prions to Abnormal Prions



Abnormal prion protein (PrP^{Prs}) molecules (β -sheet isoform) become physically associated with normal prion protein (PrP^{Sc}) molecules (α -helix isoform) and induce a conformational change that converts PrP^{Sc} molecules to PrP^{Prs} isoforms. The rate of conversion is influenced by the quality of the physical association between PrP^{Sc} and PrP^{Prs} molecules. When accumulation of abnormal PrP^{Prs} molecules is sufficient, clinical disease occurs. Abnormal PrP^{Prs} molecules may originate from mutated human prion protein genes (inherited or sporadic), sporadic conformational abnormalities, or exogenous sources. If conformational differences between PrP^{Sc} and PrP^{Prs} molecules prevent physical association of the isoforms, no conversion of PrP^{Sc} molecules occurs and clinical disease does not develop (lower panel).

PRION DISEASES

Bovine Spongiform Encephalopathy

This spongiform encephalopathy of cattle was first diagnosed in 1986. It begins with signs of anxiety, restlessness, and aggressive behavior, thus leading to the name "mad cow disease."^{30,31} Affected cattle range in age from 20 months to 18 years; most cases appear in cows between 2 and 8 years of age.³² As the disease progresses, the cow becomes unable to rise from a lying position, posterior ataxia develops, and body weight is lost despite normal appetite. Death usually occurs between 2 weeks and 6 months after onset of clinical symptoms.^{30,31} Disease is confirmed by postmortem examination of brain tissue. Immunohistochemistry has revealed distinct formations composed of protease-resistant prions in the diseased bovine brain, similar to prion protein plaques seen in kuru, nv-CJD, and many other TSEs.³³ Currently, no test to detect the disease in live cattle has been validated.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease is a rare, fatal, human TSE with a current worldwide incidence of about 1 case per million per year and an equal male to female incidence ratio. With few exceptions, it does not appear to have a definable geographic or ethnic distribution.^{34,35} There are 4 known types of CJD: sporadic (85% of all cases), inherited (10% to 15% of cases are inherited as an autosomal dominant trait^{11,34}), iatrogenic, and new-variant. In all types, little or no immunological activity is directed against the disease agent within the patient.³⁶ While many epidemiological risk factors have been proposed for sporadic CJD, none are definitive. Infection with PrP^{Sc}, a rare misfolding of the normal PrP^C protein, or a somatic mutation of the prion protein gene may be responsible.¹⁰ Inherited CJD has been linked to several different mutations in the human prion gene that lead to nonconservative amino acid substitutions in the protein. The first such described linkage was a proline-to-leucine substitution at position 102 shown to segregate with many cases of

Gerstmann-Sträussler-Scheinker syndrome.³⁷ In transgenic mice, genetic mutations that cause changes to the coding region of the prion gene have resulted in neurodegenerative disease, and TSEs have now been genetically linked to other mutations.^{10,38,39} Iatrogenic CJD has been traced to corneal transplantation, contaminated electroencephalographic electrode implantation, and contaminated surgical equipment.^{40,41} Cases have occurred in patients receiving human pituitary growth hormone or gonadotropin, or dura mater grafts.^{42,43}

Early in the course of the disease, most CJD patients exhibit rapidly progressive dementia, myoclonus, and pyramidal tract dysfunction. Electroencephalograms are characterized by distinctive periodic sharp wave activity. Sixty percent of patients present with ataxia, and 10% to 20% will have a purely ataxic illness.^{11,44} Almost any combination of cortical, subcortical, cerebellar, and spinal cord findings is possible; thus, rapid disease progression is often the characteristic that suggests diagnosis.⁴⁴

There are 3 distinct neuropathological characteristics of TSEs⁴⁵: (1) spongiform degeneration of neurons,⁴⁶ (2) severe astrocytic gliosis out of proportion with the degree of cell loss,⁴⁷ and (3) amyloid plaque formation.⁴⁸ In CJD, there is obvious astrogliosis and usually spongiform degeneration.¹¹ Widespread proliferation of fibrous astrocytes in the gray matter is evident. Generally, spongiform changes staining positive with antisera against PrP^{Sc} are seen in the cerebral cortex, putamen, caudate nucleus, thalamus, and the molecular layer of the cerebellum. Amyloid plaques, which also stain for PrP^{Sc}, occur in 5% to 10% of cases.⁴⁹

New Variant CJD

New variant CJD presents very different clinical and pathologic features from sporadic CJD.^{5,50} The first is age at onset of disease. While most cases of sporadic CJD occur between 60 to 65 years of age, mean age at onset of nv-CJD is 29 years.⁵¹ The clinical course of nv-CJD is more protracted than sporadic CJD (averaging 14 months compared with <1

year for sporadic CJD).⁵¹ Clinical symptoms of nv-CJD differ from traditional CJD.^{6,10} Two early features are sensory disturbance and behavioral changes (ie, withdrawal, anxiety, and depression) that progress to neurological abnormalities.⁵² Ataxia develops early and occurs in all cases, unlike the 60% of cases in sporadic CJD.^{5,51} Within weeks, a progressive cerebellar syndrome with forgetfulness and other memory impairment develops. Many patients experience apathy, weight loss, and mild insomnia. Progressive dementia occurs in all cases, but memory impairment may not be an early sign accompanying the dementia. Late in the disease, most patients develop myoclonus. Patients do not present with the electroencephalographic changes associated with sporadic CJD. Just before death, most patients have akinetic mutism and some develop cortical blindness. Notably, nv-CJD does not meet the clinical diagnostic criteria for traditional CJD.⁵¹

Neuropathological characteristics also differ in nv-CJD vs sporadic CJD (FIGURE 2). In the former, patients have significant prion plaques and uniform spongiform changes sparsely distributed throughout the cerebral cortex.^{5,6,51} The spongiform changes, neuronal loss, and astrogliosis are most visible in the basal ganglia and thalamus. The most striking neuropathological feature is prion plaques,⁵ which are distributed throughout the cerebrum, and particularly in the cerebellum, and have dense eosinophilic centers and pale periphery. The plaques, which all stain well for prion, are surrounded by regions of spongiform change.⁵

Currently, all types of CJD can only be diagnosed postmortem.¹¹ However, 2 antemortem techniques have been proposed. Detection of the 14-3-3 brain protein marker in the cerebrospinal fluid of patients correlates well with sporadic CJD,⁵³ while detection of the nv-CJD prion protein in the tonsils of affected individuals correlates with nv-CJD.⁵⁴ The availability of monoclonal antibodies that distinguish the PrP^{Sc} isoform from the PrP^C isoform may facilitate development of a diagnostic antemortem test.^{55,56}

Transmission of the Prion Diseases

Natural and experimental TSE transmission has occurred from cattle to cats, sheep, goats, pigs, marmosets, mice, and other cattle.⁵⁷ Human TSEs can be experimentally transferred to chimpanzees, squirrel monkeys, marmosets,¹⁰ and other humans (eg, iatrogenic CJD and kuru).^{2,38} A "species barrier"—caused by conformational differences between the prion proteins in different species—prevents transmission of disease from one species to another.^{43,59} If the differences between infecting prion and host prion are substantial, the incubation period (when conversion of host prions occurs) will be very long, or conversion may not occur. The prion strain responsible for scrapie differs substantially from human prion protein in conformation, which may explain why scrapie has never transferred to humans.^{10,34,35} Conversely, a less rigorous species barrier of the BSE prion may be one reason why BSE can be transferred to many species.^{57,60} A species barrier may be circumvented via passage of the prion protein through another species^{10,61}; for example, the passage of the scrapie PrP^{sc} into cattle may result in a cattle-adapted PrP^{sc} that causes BSE, which in turn may now infect humans.

Certain organs contain more infectious prions than others.⁶² The World Health Organization (WHO) and the Office International des Epizootics have categorized organs into 4 risk groups (TABLE),^{63,64} which are now used internationally in policies concerning BSE and CJD. The route of PrP^{sc} introduction into the host is also an important determinant of transmissibility.⁶² Direct administration into the central nervous system is the most infectious route,⁶² followed by administration into blood vessels, and intraperitoneal, intramuscular, and subcutaneous exposure. Oral ingestion is less efficient than the parenteral routes.^{62,64} Finally, the dose of infectious material is an important determinant of transmissibility.⁶² However, little research has been done to establish minimum infectious doses for humans. There is no ethical way to

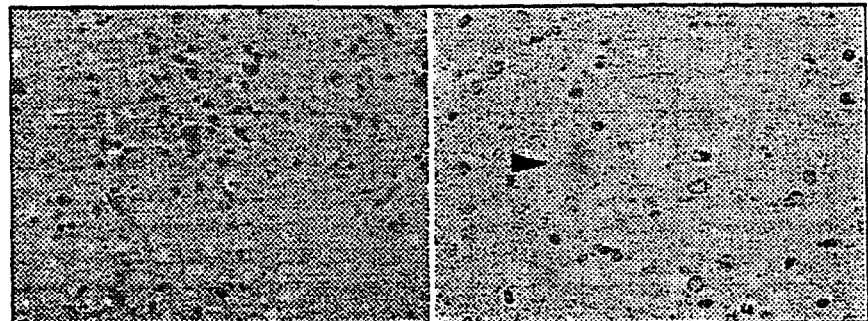
compare the lethal dose in humans with an equivalent titer in animals, but the iatrogenic transmission of CJD via incompletely decontaminated stereotactic electrodes suggests that the minimum infectious dose is probably small.⁴¹ Of course, the dose needed to transfer disease will also be critically dependent on the route of administration, with high infectivity routes most likely requiring smaller inoculum.

Mammal-to-Human Transmission: Is nv-CJD BSE in Humans? Because scrapie has never infected humans, initially there was little concern about the transfer of BSE to humans. Evidence now demonstrates that the prion responsible for BSE may be the same prion responsible for nv-CJD.^{63,66} Inbred mouse lines infected with different strains of the PrP^{sc} agent have distinct, reproducible incubation times and pathological characteristics that have been summarized into specific "signatures" for the strains.⁶⁷

Using these "signatures," Bruce et al⁶⁵ demonstrated that the PrP^{sc} strain was (1) the same in the 3 nv-CJD cases they examined, (2) different from the strains identified in sporadic cases of CJD, and (3) indistinguishable from the strain that causes BSE. Hill and colleagues⁶⁸ used the unique glycoform profiles that result after treatment of PrP^{sc} with proteinase K and found no difference in profile between the BSE PrP^{sc} and the nv-CJD PrP^{sc} . They also demonstrated that transgenic mice expressing human PrP^{sc} developed similar disease when infected with either the cattle BSE PrP^{sc} or nv-CJD PrP^{sc} .⁶⁶ This suggests that nv-CJD is a new variant of CJD and results from transmission of the BSE PrP^{sc} from infected cattle to humans.

As of January 31, 1999, there have been 39 cases of nv-CJD in the United Kingdom and 1 case in France.^{30,69} These individuals probably contracted the disease agent via oral ingestion of BSE-

Figure 2. Histopathology of Creutzfeldt-Jakob Disease and New Variant Creutzfeldt-Jakob Disease



Left, Typical spongiosis of the neuropil in the temporal cortex of a patient with Creutzfeldt-Jakob disease (hematoxylin-eosin, original magnification $\times 400$). Photomicrograph courtesy of Carlos A. Pardo, MD, Johns Hopkins University School of Medicine, Baltimore, Md. Right, Cerebral cortex of a patient with new variant Creutzfeldt-Jakob disease containing 3 characteristic florid plaques with a dense core (arrowhead) surrounded by radiating fibrils and a halo of spongiform change (periodic acid-Schiff stain, original magnification $\times 120$). Photomicrograph courtesy of James W. Ironside, National Creutzfeldt-Jakob Disease Surveillance Unit, Edinburgh, Scotland.

Table. Prion Infectivity of Different Tissue and/or Organ Types

Tissue and/or Organ Category	Infectivity	Tissues and/or Organs Included in This Category
1	High	Brain, spinal cord, eye
2	Medium	Ileum, lymph nodes, proximal colon, spleen, tonsil, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary gland, adrenal gland
3	Low	Distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus
4	Not detectable	Blood clot, feces, heart, kidney, mammary gland, milk, ovary, saliva, salivary gland, seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, fetal tissue, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine

contaminated beef prior to the UK bovine-specified risk materials (SRM) ban in 1989.^{6,22,65} This ban prohibited the entry of high-risk cattle tissues (eg, brain and spinal cord) into the human food chain at any point.^{57,70} The extent to which the human population might be affected by nv-CJD is still unknown. Using several different assumptions for risk analysis, as few as 75 to as many as 85 000 total human infections have been estimated.⁷¹ The current pattern would predict hundreds of human infections, assuming a 10-year incubation period.⁷¹ The likelihood of new human infection with the BSE prion after the bovine SRM ban in 1989 is low.

THE UK BSE EPIDEMIC

The total number of BSE cases in all of Europe (626) is almost 3 orders of magnitude less than the total number in the United Kingdom (173 126),⁷² suggesting that unique conditions existed in the United Kingdom for the BSE outbreak to have occurred. A major epidemiological study of BSE in the United Kingdom determined that it is an extended common source epidemic.³¹ The only identifiable common factor in BSE-infected cows was the consumption of cattle feed manufactured from meat and bone-meal (MBM) that contained ruminant-derived protein.³¹ It is suspected that MBM contaminated by a TSE agent was the source of BSE and that the original TSE agent is either scrapie or a cattle-adapted strain of scrapie.³¹

Meat and bonemeal is produced by rendering animal by-products (eg, offal, fat trimmings, bones from slaughterhouses, and carcasses from farms) to produce fats (tallow) and an incompletely processed, protein-rich, solid residue called *greaves*. In the 1970s, *greaves* were further processed by hydrocarbon solvent extraction and steam desolventizing to yield MBM,⁷³ which was used as a protein source in animal feed, particularly cattle feed. Between 1977 and 1982, centrifugation and pressing replaced the solvent extraction process.⁷⁴ Unfortunately, while the solvent extraction process significantly reduces the amount of infec-

tious prions in MBM, centrifugation and pressing does not.^{57,73,74}

BSE Risk Factors

The United States Department of Agriculture (USDA) and epidemiologists identified 5 risk factors in the United Kingdom that led to the BSE problem.^{74,75} First, the country has a large sheep population relative to the cattle population. Second, the uncontrolled scrapie incidence rate in these sheep is high; hence, a large reservoir of TSE prions is present to potentially infect cattle, and, prior to 1988, carcasses of sheep that died of scrapie and other causes constituted a significant part of the raw material used by UK rendering plants to produce animal feed.^{6,74} Third, reduced use of hydrocarbon solvent extraction in MBM production resulted in large amounts of BSE or scrapie-contaminated MBM.^{57,73} Fourth, extensive use was made of MBM from *greaves* that contained large concentrated amounts of the BSE or scrapie prion due to the partial rendering of the raw material.⁷³ Fifth, MBM constituted 4% to 5% of the diet of dairy calves; consequently, more than 60% of UK dairy herds developed at least 1 case of BSE.⁷⁶

Once BSE was established, the feeding of large amounts of rendered BSE-infected cattle products back to calves fostered the epidemic. This recycling of the BSE agent from adult cattle to calves probably continued until ruminant-to-ruminant feeding was banned in 1988.

Development of nv-CJD in the United Kingdom

Before any action was taken to contain BSE, contaminated bovine products could have entered the human food chain, eg, through SRM contamination of processed beef.^{1,22,77} At the time, there was no evidence that the scrapie agent could cause human infection after passage in cattle^{22,34,35,78} and there was no evidence to predict that the BSE prion species barrier would be less rigorous between cattle and humans. In fact, an analysis of the ability of the BSE PrP^{Sc} agent to convert human PrP^{Sc} into PrP^{Sc} suggested that the transmission risk was

low.⁷⁹ However, this in vitro experiment could not consider in vivo effects such as dose of inoculum and route of infection, which play a role in transmission. Thus, the lack of scientific data on the cattle-to-human species barrier, the long interval between the consumption of the BSE prion and the appearance of nv-CJD, and perhaps the slow response to the emerging problem all played roles in the current appearance of BSE and nv-CJD in the United Kingdom.

UK and European Union Policies and Regulations to Control BSE and nv-CJD

Internationally, 3 approaches are used to control nv-CJD: (1) minimizing the risk of further contamination of cattle with BSE, (2) eradicating any existing BSE cases, and (3) eliminating human exposure to the BSE agent. Due to the severity of the UK problem, British policies are the most stringent, although policies of the European Union (EU) are similar.

Animals and Animal Products. In 1988, the United Kingdom made BSE a reportable disease and required that all suspect cattle be killed, sent for diagnosis, and then incinerated.⁵⁷ Cattle farmers are compensated to ensure compliance.

The EU's policy requires destruction of the entire herd in which a suspect cow is found.⁸⁰ The EU allows importation of UK deboned beef and beef products if produced under specific export conditions,⁸¹ and there are detailed guidelines on the sourcing of imported materials to eliminate potentially BSE-infected products.^{80,82-84}

In the United Kingdom, all adult animals designated for slaughter are first examined to ensure that no suspected BSE cases are slaughtered for human consumption.⁷⁰ Bovine spongiform encephalopathy prions have been detected only in certain organs (ie, SRM). To prevent transmission into animals or humans, the SRM, which include the head (excluding the tongue), spinal cord, spleen, and tonsils of cows aged 6 months or older, and the intestines and thymus of all cows, are removed at slaughter and discarded. Specified risk materials of cattle

older than 6 months have been banned from human food since 1989 and from animal feed since 1990.^{70,77}

The United Kingdom and EU prohibit the use of any mammalian protein in ruminant feed.^{77,82,84,85} Incorporation of mammalian MBM in any farmed-animal feed (including fish) has been banned in the United Kingdom since 1996, thereby eliminating potential cross-contamination of cattle feed.⁸⁵ Since the BSE agent does not transmit laterally, ie, directly from cow to cow, and transmission from mother to calf accounts for no more than 10% of expressed disease, the feed ban measures should eventually eradicate the disease in cattle.³² To ensure compliance, the United Kingdom implemented a rigorous sampling program in 1996 to examine a large number of premises that handle animal feed. These efforts have been remarkably successful: the rate of new BSE infections has declined 40% per year.³²

Products for Human Consumption. Most emphasis has been on preventing human consumption of potentially infected bovine material; hence, the EU introduced legislation, effective January 2000, prohibiting the use of SRM for any purpose.^{82,84,86} However, concern about effects on pharmaceutical and cosmetics production, as well as new scientific data, have prompted development of a new proposal.⁸⁴ The EU may issue separate rules for drugs to exempt that sector from any future directives.⁸⁷ Until the EU submits a new proposal for EU-wide SRM controls, current national measures remain in place. Since March 1997, UK legislation prohibits use of SRM in cosmetic, pharmaceutical, and medical products.⁸⁸ In December 1997, the United Kingdom initiated a requirement that all beef be deboned, based on data indicating that the BSE agent could be detected in the dorsal root ganglia and bone marrow of cows older than 30 months.⁸⁹

Because no infectivity has been detected in cow's milk, it has been deemed safe for human consumption.⁶⁴ On March 23, 1999, the EU's Scientific Steering Committee reconfirmed this conclusion but added that, "as a pre-

cautionary measure," milk from BSE-affected cows should not be used.⁹⁰

Human Tissues. The National CJD Surveillance Unit (Edinburgh, Scotland), where the first cases of nv-CJD were described in 1995,⁵ monitors the appearance of CJD cases in the United Kingdom and the extent of human disease resulting from the BSE epidemic. Using data from this unit, the Spongiform Encephalopathy Advisory Committee advises the UK government on policies pertaining to CJD and nv-CJD cases.

Blood. Although WHO and the EU state that transmission of CJD via blood cannot currently be confirmed^{91,92} and too few data on nv-CJD transmission exist to make recommendations,^{64,84} they advocate exclusion of blood donation by people who have or are at risk for CJD.^{64,84} The possibility that nv-CJD might be transferred via lymphoreticular tissue (eg, white blood cells) is under study.⁹³ Because white blood cells may possess the highest CJD infectivity of all blood components,⁹⁴ the United Kingdom began leukodepleting all blood donations in July 1998.⁹⁵ Recent data suggest potential but minimal risk of contracting CJD from plasma fractions⁹⁴; hence, plasma pools containing plasma from CJD-infected donors have not been recalled in Europe. However, in 1997 the United Kingdom began recalling all plasma if contamination from nv-CJD-infected donors was suspected.⁹⁶ The lack of satisfactory scientific data emphasizes the need for continued research.

WHY BSE HAS NOT BEEN FOUND IN THE UNITED STATES

The United Kingdom has more than 40 million sheep compared with 8 million in the United States. In addition, the United Kingdom had only 12 million head of cattle (prior to the BSE outbreak) compared with more than 104 million in the United States.⁷² Because BSE probably originated from feeding cattle MBM contaminated by sheep scrapie prions,³¹ the lower sheep-to-cattle ratio in the United States significantly reduces the potential reservoir of infective agent. In fact, US-rendered animal pro-

tein has only 0.6% sheep-derived protein compared with 14% in the United Kingdom.⁶ Furthermore, the strains of scrapie infecting US sheep may not be capable of overcoming the species barrier as the scrapie strain in the United Kingdom probably did.⁶ There also may be a lower incidence of scrapie in US sheep because the United States has had a scrapie control program since 1952.⁶ Finally, the United States is a major producer of plant-based protein such as soybean meal, and in contrast to the United Kingdom, plant-based proteins are a major part of complete animal feeds in this country.⁷⁵

Although BSE has never been found in US cattle, there is speculation that it already exists at very low levels and has simply not been detected.⁶ In one experiment, cows infected intracranially, but not orally, with US scrapie prions developed a form of TSE.⁹⁷ However, this TSE lacked the characteristic spongiform neuropathological characteristics of natural BSE cases in the United Kingdom.⁹⁷ Furthermore, neuropathological examinations of more than 7600 US cattle diagnosed with neurological disorders since 1990 have not revealed a case of BSE.⁹⁸

US POLICIES AND REGULATIONS TO PREVENT BSE

The USDA and its associated Animal and Plant Health Inspection Service (APHIS) regulate and provide guidance on the importation of plant and animal materials. They are involved in surveillance for BSE in the United States and in educating the agricultural sector about BSE. The Food and Drug Administration (FDA) regulates the content of animal feed and the content of any product used for human consumption. Although responsibility for meat, poultry, and egg products (as opposed to shell eggs) is shared, the Food Safety Inspection Service of the USDA primarily regulates these products.

Animals and Animal Products

Bovine spongiform encephalopathy could theoretically occur in US cattle be-

cause TSEs that could potentially transfer to cattle exist in this country (ie, scrapie in sheep and goats, transmissible mink encephalopathy in farmed minks, and chronic wasting disease in deer and elk).^{99,100} Without regulation, the disease agent could be transmitted via the feeding of processed ruminant proteins to cattle. Also, the long incubation period for BSE would mask amplification, resulting in greater animal exposure to BSE, which is exactly what transpired in the United Kingdom. To prevent this, the US government has implemented several regulations based on the 4 basic assumptions of hazard identification, risk assessment, risk management, and risk communication.¹⁰¹

In 1989, APHIS banned the importation of live ruminants and most ruminant products from the United Kingdom and all other countries reporting BSE.¹⁰² The United States has not imported beef from the United Kingdom since 1985, and since 1991 APHIS has required that all imported meat and edible products for human or animal consumption from ruminants of the bovine family be deboned and that visible lymph and nervous tissue be removed.⁹⁸ Additionally, imported meat and edible products must be from animals that have undergone a veterinary examination before slaughter. These animals also must not have been in any country in which BSE was reported when that country permitted the use of ruminant protein in ruminant feed. In December 1997, this ban was expanded to prohibit importation of all live ruminants and most ruminant products from all European countries.¹⁰³ APHIS uses the Office International des Epizootics' guidelines to categorize countries according to BSE risk, and importation of live ruminants and ruminant products from countries with known BSE risk or unknown BSE status is prohibited (L. Detwiler, DVM, USDA-APHIS, written communication, March 25, 1999).

To prevent amplification of BSE should it exist at undetected levels in the cattle population, a 1997 FDA regulation prohibits the use of protein derived from mammalian tissue in feed for ruminant

animals, with some exemptions.¹⁰⁴ The exemptions are for pure swine or pure equine proteins, blood and blood products, gelatin, feeds processed from restaurant waste, and milk and milk products. Pigs and horses have never been identified with a naturally occurring TSE. Blood and milk were exempted because they have not been found to transmit the infectious prion protein. WHO and EU policies also exempt swine and equine products, blood, and milk.^{64,80,82}

Compliance by individuals and establishments responsible for feeding ruminants is critical.⁷⁵ The FDA will ultimately inspect nearly 100% of the establishments that produce, process, manufacture, or distribute ruminant-derived protein intended for feeding of animals. Some farms, feedlots, and ranches where ruminants are raised are being inspected to determine whether animals are being fed prohibited ruminant-derived proteins. The FDA Center for Veterinary Medicine has redirected one fourth of its field resources to accomplish this goal (S. Nightingale, MD, FDA, written communication, August 23, 1998).

Because immediate detection of any potential BSE case in US cattle is essential, APHIS aggressively educates veterinarians, the beef industry, farmers, and producers on the clinical and pathological signs of BSE.⁹⁸ Hundreds of cattle brains are examined each year from animals that displayed neurological signs at or before slaughter.⁹⁸ In addition, cattle are examined at all federally inspected slaughter establishments, and inspectors are alert for central nervous system disorders. Suspect animals are killed and tested. As of January 1999, more than 7600 brains had been examined from cattle demonstrating neurological deficit and no cases of BSE were detected.⁹⁸

USDA Response Plan provides a step-by-step outline of actions to be taken if BSE is detected in the United States, including identification of the suspect animal, confirmation, epidemiological investigation, and animal and herd disposal.⁹⁸ In April 1998, the USDA announced a 2-year cooperative effort with Harvard University School of Public

Health to evaluate the USDA's current BSE prevention measures, review current scientific information, assess the ways that BSE could potentially enter the United States, and identify possible additional measures to protect human and animal health.¹⁰⁵ Altogether, the US government has taken substantial steps to ensure that BSE will not spread in US cattle should it ever emerge. Despite this, criticisms of the government's efforts include a failure to act more rapidly, the need for a more stringent ban on feeding of any mammalian protein to any other animal species, and failure to include blood and milk and their respective products in the 1991 ban.

Products for Human Consumption

The absence of BSE in the United States implies that there is already minimal risk for nv-CJD. This is reinforced by the fact that no cases with the distinctive characteristics of nv-CJD have been identified either by current surveillance studies or on review of clinical and neuropathological hospital records.¹⁰⁶ However, to ensure public health, the FDA developed guidelines regarding the use of gelatin in drugs and biologics.¹⁰⁷ Still being evaluated are the more than 300 health products derived from bovine sources, including collagen and bovine pericardium for cardiovascular devices, bone fillers, cortical shields, and contact lens disinfectants.¹⁰⁸ Additionally, many biologic substitutes and therapy alternatives using human organs, tissues, and cells require the use of bovine-derived products. The FDA Center for Drug Evaluation and Research ensures the safety of drugs containing active ingredient(s) derived from cattle through the application approval process (S. Nightingale, MD, FDA, written communication, August 23, 1998).

Gelatin. The TSE Advisory Committee, an expert panel similar to the United Kingdom's Spongiform Encephalopathy Advisory Committee, recently noted that scientific evidence no longer justifies exempting gelatin from FDA regulations on bovine-derived material. New guidelines now require that the tissue, species, and source country

of the raw material for gelatin be determined.¹⁰⁷ Gelatin derived from the bones and hides of cattle from BSE-affected countries or countries of unknown BSE status is prohibited from use in injectable, implantable, or ophthalmic products. Oral and cosmetic use of such gelatin is acceptable only if the cattle are from herds without BSE and the SRMs are removed immediately after slaughter. Bovine hide gelatin can be used in foods and cosmetics only if hides from cattle with central nervous system symptoms are excluded and contamination with central nervous system and eye tissues is avoided. Gelatin derived from raw materials from the United States and other countries without BSE can be used. In 1998, the WHO Scientific Steering Council made similar policy recommendations.⁸⁰

Specified Risk Materials. In the absence of BSE in US cattle, no restrictions have been issued by the FDA or the USDA on the use of SRM in products for human consumption.

WHO recommends that all countries conduct a BSE risk assessment and develop their own risk management strategies. Laws banning certain bovine materials from human consumption, when they exist, must be adhered to rigidly.⁶⁴

Human Tissues

Blood. There is conflicting and disputed evidence that the blood of subjects with CJD or other TSEs or incubating TSEs is infectious. Epidemiological studies show no evidence that transmission can occur through blood.^{91,92} Additionally, no cases of transfusion-related CJD have ever been reported in humans, even those with hemophilia.¹⁰⁹ Experimental data indicate that the transfer of spleen, liver, or lymph node materials from CJD patients into primates results in disease, yet the transfer of blood from CJD patients into primates does not.⁹² On the other hand, the transfer of TSE-infected rodent blood into rodents definitely causes disease.⁹² Therefore, the FDA has adopted an extremely conservative approach to guidelines on blood and blood products.

In general, FDA guidelines call for the withdrawal and quarantine of CJD-implicated blood and blood products, excluding plasma derivatives.¹¹⁰ Because of the lack of data on nv-CJD transmission via plasma, FDA guidelines require nv-CJD-implicated plasma derivatives to be withdrawn.¹¹¹ The FDA classifies blood donors into the following risk categories: (1) diagnosed as having TSE, (2) at increased risk due to familial TSE, (3) at increased risk for iatrogenic TSE, (4) at possibly increased risk due to TSE in a single family member (probably sporadic), and (5) at no increased risk. The FDA suggests donors in risk categories 1 through 4 be excluded from donating blood,^{110,111} and recommends that source plasma from donors later diagnosed as having CJD or donors at risk of developing CJD be quarantined and destroyed.^{110,111} While definitive conclusions on the safety of blood and blood products require additional scientific data, a conservative course of action is prudent.

CONCLUSIONS

Data suggest that nv-CJD results from transmission of the BSE prion to humans.^{65,66} In the United Kingdom, human infection with nv-CJD probably resulted from ingestion of BSE-contaminated beef.⁷⁷ In public health terms, these links are compelling enough to warrant action by relevant US authorities. However, because BSE has not been observed in the United States as of March 1999,^{8,98} most government policies are based on risk-management principles.

Assuming that BSE can be transferred to humans as nv-CJD, determination of risk to US residents depends on whether parts of a cow carrying infectious prions can be consumed by humans as food, medication, biological products or devices, or cosmetics. The risk of contracting a human TSE, such as nv-CJD, from cattle in the United States currently is minimal for the following reasons. First, no known cases of BSE exist.^{6,98} Any potential human contact with the disease agent would have to come from the importation of contaminated cattle products or exposure while

traveling in BSE-infected countries. Second, adequate guidelines exist to prevent high-risk bovine materials from contaminating products intended for human consumption.^{107,110} The only possible exception is the lack of guidelines for the oral consumption of SRMs. Third, adequate regulations exist to prevent undetected cases of BSE (if any) from uncontrolled amplification in US cattle.^{98,104} Finally, adequate regulations exist to prevent entry of foreign sources of BSE, either as live cattle or as bovine-derived products, into the United States.^{98,102,103}

RECOMMENDATIONS

The following statements, recommended by the American Medical Association (AMA) Council on Scientific Affairs, were adopted as AMA policy in December 1998.

The AMA:

1. Supports the current FDA guidance/regulations regarding the treatment of products from bovine sources destined for human utilization, and the treatment of blood products from potential CJD donors.

2. Recommends the FDA and the USDA continue to aggressively enforce regulations in place to prevent the occurrence/transmission of BSE in the United States.

3. Recommends the FDA, USDA, and Department of Health and Human Services continue to evaluate scientific data on TSEs and incorporate this information into their guidance and regulations.

4. Recognizes that the public may be concerned about BSE risks; therefore, the AMA recommends that physicians become knowledgeable about BSE so that they can appropriately advise their patients about routes and risks of BSE transmission, especially that the consumption of brain and spinal cord from infected animals would carry the highest risk of transmission to humans, and that persons who are traveling abroad should refrain from consuming brain and spinal cord from cattle unless they know that the countries in which they are traveling are free of BSE.

5. Recommends increased surveillance of new CJD cases as they arise in order to monitor for the possible appearance of nv-CJD via: (a) Referral of all deaths due to suspected CJD to an appropriately qualified pathologist for autopsy, with the submission of autopsy reports of confirmed cases to the Prion Disease Pathology Surveillance Center at Case Western Reserve University, which is collaborating with the Centers for Disease Control and Prevention; (b) Reporting of the diagnosis of CJD on the death certificate in all cases and the strengthening of the current system enabling health authorities to obtain clinical or pathological data on the CJD cases of greatest public health concern; (c) Prompt notification of any case of nv-CJD to both the appropriate state health department and the Centers for Disease Control and Prevention.

6. Recommends that well-controlled research be performed in the following areas: (a) Elucidation of the mechanism of disease of TSEs; (b) Elucidation of the infectivity, dose requirements, and clearance of the disease agent to provide more data for adequate risk analyses of disease transmission; (c) The risk of transmission via blood and blood products; (d) Alternatives to the use of bovine-derived products in drug manufacture and other biologic industries; (e) Antemortem diagnosis of BSE and nv-CJD and the detection and inactivation of the disease agent in blood supplies.

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